PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 August 1998 (12.08.98)	
International application No. PCT/US97/18348	**Applicant's or agent's file reference** UTFC550P--
International filing date (day/month/year) 03 October 1997 (03.10.97)	**Priority date** (day/month/year) 04 October 1996 (04.10.96)
Applicant TORMO, Mar et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 May 1998 (04.05.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Ingrid Hours
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: TIMOTHY S. CORDER
ARNOLD, WHITE & DURKEE
P.O. BOX 4433
HOUSTON, TX 77210

REC'D.-A.W.&D.
JAN 19 1998
INTERNATIONAL DEPT

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference UTFC550P-	Date of Mailing *(day/month/year)* 14 JAN 1998 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US97/18348 RECEIVED INT'L. DEPT. JAN 20 1998	International filing date *(day/month/year)* 03 OCTOBER 1997
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM A,W,&D. AUSTIN U.S. case 550P-- docketed File Foreign Search for 2-14-98 by DB / JAB	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT SCHWARTZMAN Telephone No. (703) 308-0196

Form PCT/ISA/220 (January 1994)★

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference UTFC550P-	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US97/18348	International filing date *(day/month/year)* 03 OCTOBER 1997	(Earliest) Priority Date 04 OCTOBER 1996
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18348

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/127, 31/70; C07H 21/04; C12N 15/00
US CL : 424/450; 435/172.3, 375; 514/44; 536/24.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 435/172.3, 375; 514/44; 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: Medline, Biosis, Embase, CAPlus, WPIDS, JAPIO, PATOSEP, PATOSWO
search terms: bcl-2, antisense, lipd, liposome

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 93/20200 A1 (IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED) 14 October 1993, page 7, lines 10-29; page 15, lines 16-23; page 18, lines 26-30; page 59, lines 6-7.	1-6, 9 -- 7,8
X -- Y	WO 95/08350 A1 (BROTMAN, HARRIS, F. et al.) 30 March 1995, page 3, lines 2-22; page 13, lines 2-5; page 14, lines 16-25.	1-6 -- 7, 8
X	ALMAZAN et al. Methylphosphonate-containing oligonucleotides efficiently and specifically inhibit Bcl-2 and erbB-2 expression in vitro. Proc. Amer. Assoc. Cancer Res. March 1996, Vol. 37, page 353 Abstract No. 2407, see entire document.	1, 2

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
10 DECEMBER 1997

Date of mailing of the international search report
14 JAN 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
ROBERT SCHWARTZMAN
Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18348

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	TORMO et al. Antitumor activity of liposomal-bcl-2-antisense oligonucleotides in follicular lymphoma. Proc. Amer. Assoc. Cancer Res. March 1996, Vol.37, page 173, Abstract No. 1190, see entire document.	1, 2, 5, 6 -- 7, 8
Y	LEDLEY, F.D. Non-viral gene therapy. Curr. Opin. Biotechnol. 1994, Vol. 5, pages 626-636, see entire document.	7, 8
A	ROJANASAKUL, Y. Antisense oligonucleotide therapeutics: drug delivery and targeting. Adv. Drug Delivery Rev. 1996, Vol.18, pages 115-131, see entire document.	1-20

PCT
REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* UTFC550P--

Box No. I TITLE OF INVENTION
INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXY NUCLEOTIDES

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM
201 West 7th Street
Austin, Texas 78701
United States of Texas

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

TORMO, Mar
Guillem Sorolla, #36
Valencia, Spain

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: ES

State *(i.e. country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by give name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CORDER, Timothy S.
ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, TX 77210
United States of America

Telephone No. (512) 418-3000

Facsimile No. 713-789-2679

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

TARI, Ana M.
7500 Kirby Drive, #311
Houston, Texas 77030
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: PT

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

LOPEZ-BERESTEIN, Gabriel
122 Bellaire Court
Bellaire, Texas 77602
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

MCDONNEL, Timothy J.

United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated Sates except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☐ **AP ARIPO Patent: GH** Ghana, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☐ **EA Eurasian Patent: AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP European Patent: AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ **OA OAPI Patent: BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☐ **AL** Albania
☐ **AM** Armenia
☐ **AT** Austria
☐ **AU** Australia
☐ **AZ** Azerbaijan
☐ **BA** Bosnia and Herzegovina
☐ **BB** Barbados
☐ **BG** Bulgaria
☐ **BR** Brazil
☐ **BY** Belarus
☒ **CA** Canada
☐ **CH** and **LI** Switzerland and Liechtenstein
☐ **CN** China.
☐ **CU** Cuba.
☐ **CZ** Czech Republic
☐ **DE** Germany
☐ **DK** Denmark
☐ **EE** Estonia
☐ **ES** Spain
☐ **FI** Finland
☐ **GB** United Kingdom
☐ **GE** Georgia
☐ **GH** Ghana
☐ **HU** Hungary
☐ **ID** Indonesia
☐ **IL** Israel
☐ **IS** Iceland
☒ **JP** Japan
☐ **KE** Kenya
☐ **KG** Kyrgyzstan
☐ **KP** Democratic People's Republic of Korea
☐ **KR** Republic of Korea
☐ **KZ** Kazakstan
☐ **LC** Saint Lucia
☐ **LK** Sri Lanka
☐ **LR** Liberia
☐ **LS** Lesotho
☐ **LT** Lithuania
☐ **LU** Luxembourg
☐ **LV** Latvia
☐ **MD** Republic of Moldova
☐ **MG** Madagascar
☐ **MK** The former Yugoslav Republic of Macedonia
☐ **MN** Mongolia
☐ **MW** Malawi
☐ **MX** Mexico
☐ **NO** Norway
☐ **NZ** New Zealand
☐ **PL** Poland
☐ **PT** Portugal
☐ **RO** Romania
☐ **RU** Russian Federation
☐ **SD** Sudan
☐ **SE** Sweden
☐ **SG** Singapore
☐ **SI** Slovenia.
☐ **SK** Slovakia
☐ **SL** Sierra Leone
☐ **TJ** Tajikistan
☐ **TM** Turkmenistan
☐ **TR** Turkey
☐ **TT** Trinidad and Tobago
☐ **UA** Ukraine
☐ **UG** Uganda
☒ **US** United States of America (C.I.P.)
☐ **UZ** Uzbekistan
☐ **VN** Viet Nam
☐ **YU** Yugoslavia
☐ **ZW** Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☐ .....
☐ .....
☐ .....
☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designations(s) of _____. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box ***If the Supplemental Box is not used, this sheet need not be included in the request.***

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e., country) of residence if no State of residence is indicated below:*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named persons is inventor;*
(iv) if, in addition to the agent(s) indicated in box No. Iv, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits, of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	*in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty: and furnish that statement below.*

CONTINUATION OF BOX NO. V:

US: 08/726.211; 4 OCTOBER 1996 (04.10.96)

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) US	4 October 1996 (04.10.96)	08/726.211	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1

BOX No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / US

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date:	Number:
US	4 October 1996 (04.10.96)	08/726.211

BOX No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 5 sheets
2. description	: 53 sheets
3. claims	: 2 sheets
4. abstract	: 1 sheets
5. drawings	: 8 sheets
Total:	: 69 sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *(identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☒ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other (specify): **post card, check, Statement of Conformity**

Figure No. _____ of the drawing (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

ARNOLD, WHITE & DURKEE

Timothy S. Corder, Applicant's Agent — Date: 10.3.97

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: : [ ] received: [ ] not received
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. [ ] Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: DAVID L. PARKER
ARNOLD, WHITE & DURKEE
P.O. BOX 4433
HOUSTON, TX 77210

REC'D. - A. W. & D.
SEP 2 8 1998
INTERNATIONAL DEPT.

PCT

RECEIVED
A.W. & D.
AUSTIN, INT.L
SEP 29 1998

WRITTEN OPINION
(PCT Rule 66)

Date of Mailing *(day/month/year)*	25 SEP 1998
Applicant's or agent's file reference: UTFC550P--	REPLY DUE: within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US97/18348	03 OCTOBER 1997	04 OCTOBER 1996

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [X] Certain observations on the international application

DOCKETED [X] UPDATED [ ]
Previously ___ Not Required ___
Action Required: Status will be done / Rsp to OA re-written opin.
DATE DUE: 11/25/98
By: ___ Checked: ___

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04 FEBRUARY 1999

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ROBERT SCHWARTZMAN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (January 1994)*

WRITTEN OPINION

International application No.
PC[redacted]97/18348

I. Basis of the opinion

1. This opinion has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

[X] the international application as originally filed.

[X] the description, pages 1-53 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.

[X] the claims, Nos. 1-20 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-12 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

3. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:
NONE

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	7, 8, 10-20	YES
	Claims	1-6 and 9	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-20	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-6 and 9 lack novelty under PCT Article 33(2) as being anticipated by Imperial Cancer Research Technology Limited (WO 93/20200).

Imperial Cancer Research Technology Limited (WO 93/20200) teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). The antisense oligonucleotide can be synthesized from an expression construct encoding the oligonucleotide (page 18, lines 26-30). The antisense oligonucleotide or expression construct is preferably delivered into cells as a composition comprising a liposome (page 59, lines 6-7).

Claims 1-6 lack novelty under PCT Article 33(2) as being anticipated by Brotman, Harns, F. (WO 95/08350).

Brotman, Harns, F. (WO 95/08350) teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 3, lines 2-22). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO:1 (page 13, lines 2-5). The antisense oligonucleotide is preferably delivered into cells as a composition comprising a liposome (page 14, lines 16-25).

Claims 1, 2, 5 and 6 lack novelty under PCT Article 33(2) as being anticipated by Tormo et al.

Tormo et al. teaches an antisense polynucleotide targeted to Bcl-2. This polynucleotide was incorporated into liposomes.

Claims 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. in view of Ledley.

(Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 10-20 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s):

Claims 10-20 are vague and indefinite as it is not clear what is meant by inhibiting a disease (e.g., does it mean cure, slow down disease progression,decrease viability of diseased cells, etc.). Additionally, claim 10 is vague and indefinite as it does not provide a positive process step which clearly relates back to the preamble.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 9/127, 31/70; C07H 21/04; C12N 15/00 and US Cl.: 424/450; 435/172.3, 375; 514/44; 536/24.5

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Imperial Cancer Research Technology Limited (WO 93/20200), Brotman, Harns, F. (WO 95/08350) and Tormo et al. are applied as above. None of these references teach liposomes comprising phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. Ledley teaches (pages 628-630) lipid formulations for delivery of DNA. Ledley points out that formulations comprising neutral phospholipids such as dioleolyphosphatidylethanolamine facilitate highly efficient gene transfer. It would have been prima facie obvious to one of ordinary skill in the art at the tine the invention was made to use liposomes to transfer an antisense Bcl-2 polynucleotide into cells as taught by Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. having a composition comprising the claimed phospholipids, motivated by the teaching of Ledley that such neutral phospholipids make highly efficient liposomes.

Claims 1-9 lack an inventive step under PCT Article 33(3) as being obvious over Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) in view of Tari et al.

Imperial Cancer Research Technology Limited (WO 93/20200), Brotman, Harns, F. (WO 95/08350) and Tormo et al. are applied as above. None of these references teach liposomes comprising phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a phospholipid selected from a phosphatidylcholine or a phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising an antisense oligonucleotide targeted to Bcl-2 encapsulated in a liposome as taught by Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. and to use the liposomal formulations taught by Tari et al., motivated by the teaching of Tari et al. that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Claims 1-3 and 5-20 lack an inventive step under PCT Article 33(3) as being obvious over Abubakr et al., Pocock et al. and Cotter et al. all in view of Tari et al.

Abubakr et al. teaches (entire document) a SCID mouse model of follicular lymphoma in which WSU-FSCCL cells, which have a t(14:18) translocation, are injected into the mice. Injection of a phosphorothioate antisense oligonucleotide 22 nucleotides long which is targeted to the translation initiation site of Bcl-2 either IP or IV into the mice 3 times a week for 2 weeks starting on day 7 following lymphoma cell injection resulted in a longer survival time and the absence of tumors.

Pocock et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. Constant infusion of an antisense oligonucleotide targeted to Bcl-2 for 14 days starting 8 days after injecting lymphoma cells prevented the development of lymphoma.

Cotter et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. When the cells were pretreated in vitro with an antisense oligonucleotide 20 nucleotides long which is targeted to the translation initiation site of Bcl-2 prior to administration to the mice the development of lymphoma was prevented.

Abubakr et al., Pocock et al, and Cotter et al., taken together, clearly show that treatment of lymphoma cells having a t(14:18) translocation with an antisense oligonucleotide targeted to the translation initiation site of the Bcl-2 gene, either

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

before or after administration to SCID mice, results in the inhibition of proliferation of the lymphoma cells and the prevention of lymphoma development in the mice. None of these references teaches administration of the antisense oligonucleotide as a composition comprising neutral lipids.

Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a neutral phospholipid selected from a phosphatidylcholine or a phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). Tari et al. teaches the benefit of using liposomes consisting of neutral lipids for the delivery of antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). It would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to use an antisense oligonucleotide targeted to Bcl-2 to inhibit the proliferation of cells having a t(14:18) translocation resulting in overexpression of Bcl-2 as taught by Abubakr et al., Pocock et al. and Cotter et al. and to administer the antisense oligonucleotide as a composition comprising a neutral phospholipid as taught by Tari et al., motivated by the teaching of Tari et al. that the neutral lipid composition imparts several benefits on the administration of an antisense oligonucleotide. It further would have been obvious to inhibit the proliferation of a lymphoma cell in a human as effects seen in immunocompromised mouse models of lymphoma and leukemia are recognized in the art to be reasonably predictive of results in humans. In terms of particular volumes, dosages and schedules of administration, one of ordinary skill in the art could practice routine optimization to determine appropriate volumes, dosages and schedules such as those that are claimed when converting treatments developed for mice into equivalent treatments for humans.

Claim 4 lacks an inventive step under PCT Article 35(3) as being obvious over Abubakr et al., Pocock et al. and Cotter et al., all in view of Tari et al. and further in view of Imperial Cancer Research Technology Limited (WO 93/20200).

Abubakr et al., Pocock et al., Cotter et al. and Tari et al. each are applied as above. These references do not teach an antisense oligonucleotide which comprises the sequence of SEQ ID NO:1. Imperial Cancer Research Technology Limited (WO 93/20200) et al. teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). It would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to make and use an antisense oligonucleotide targeted to the translation initiation site of Bcl-2 as taught by Abubakr et al., Pocock et al., Cotter et al. and Tari et al. and to have the oligonucleotide comprise the sequence of SEQ ID NO:1 as taught by Imperial Cancer Research Technology Limited (WO 93/20200) as Abubakr et al., Pocock et al., Cotter et al. and Imperial Cancer Research Technology Limited (WO 93/20200) et al. each teach the targeting of the antisense oligonucleotide to a region comprising the ATG codon of Bcl-2 and all of the references teach an oligonucleotide sequence which comprises at least part of SEQ ID NO:1. Since all of the oligonucleotides overlap and all of them have been shown to be effective they are all equivalent and one of ordinary skill in the art would reasonably expect that any antisense oligonucleotide which comprises SEQ ID NO:1 would work to lower Bcl-2 expression.

NEW CITATIONS

ABUBAKR et al. Effectiveness of BCL-2 antisense oligodeoxynucleotides (AS-ODN) against human follicular small-cleaved cell lymphoma (FSCCL)-SCID mice xenograft model. Blood. December 1994, Vol. 84, No. 10 Suppl. 1, page 374A, Abstract 784, see entire document.

POCOCK et al. In vivo suppression of B-cell lymphoma with BCL-2 antisense oligonucleotides. Blood. December 1993, Vol. 83, No. 10 Suppl. 1, page 200A, Abstract 1481, see entire document.

COTTER et al. Antisense oligonucleotides suppress B-cell lymphoma growth in a SCID-hu mouse model. Oncogene. October 1994, Vol. 9, pages 3049-3055, see entire document.

US 5,417,978 A (TARI et al.) 23 May 1995.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference UTFC550P--	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US97/18348	International filing date *(day/month/year)* 03 OCTOBER 1997	Priority date *(day/month/year)* 04 OCTOBER 1996
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04 MAY 1998	11 DECEMBER 1998
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT SCHWARTZMAN Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/18348

I. Basis of the report

1. This report has been drawn on the basis of (*Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments*):

[X] the international application as originally filed.

[X] the description, pages 1-53 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-20 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-12 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/18348

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	7, 8, 10-20	YES
	Claims	1-6 and 9	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-20	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-6 and 9 lack novelty under PCT Article 33(2) as being anticipated by Imperial Cancer Research Technology Limited (WO 93/20200).

Imperial Cancer Research Technology Limited (WO 93/20200) teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). The antisense oligonucleotide can be synthesized from an expression construct encoding the oligonucleotide (page 18, lines 26-30). The antisense oligonucleotide or expression construct is preferably delivered into cells as a composition comprising a liposome (page 59, lines 6-7).

Claims 1-6 lack novelty under PCT Article 33(2) as being anticipated by Brotman, Harns, F. (WO 95/08350).

Brotman, Harns, F. (WO 95/08350) teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 3, lines 2-22). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO:1 (page 13, lines 2-5). The antisense oligonucleotide is preferably delivered into cells as a composition comprising a liposome (page 14, lines 16-25).

Claims 1, 2, 5 and 6 lack novelty under PCT Article 33(2) as being anticipated by Tormo et al.

Tormo et al. teaches an antisense polynucleotide targeted to Bcl-2. This polynucleotide was incorporated into liposomes.

Claims 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. in view of Ledley.
(Continued on Supplemental Sheet.)

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 10-20 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s):

Claims 10-20 are vague and indefinite as it is not clear what is meant by inhibiting a disease (e.g., does it mean cure, slow down disease progression,decrease viability of diseased cells, etc.). Additionally, claim 10 is vague and indefinite as it does not provide a positive process step which clearly relates back to the preamble.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 9/127, 31/70; C07H 21/04; C12N 15/00 and US Cl.: 424/450; 435/172.3, 375; 514/44; 536/24.5

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Imperial Cancer Research Technology Limited (WO 93/20200), Brotman, Harns, F. (WO 95/08350) and Tormo et al. are applied as above. None of these references teach liposomes comprising phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. Ledley teaches (pages 628-630) lipid formulations for delivery of DNA. Ledley points out that formulations comprising neutral phospholipids such as dioleolyphosphatidylethanolamine facilitate highly efficient gene transfer. It would have been prima facie obvious to one of ordinary skill in the art at the tine the invention was made to use liposomes to transfer an antisense Bcl-2 polynucleotide into cells as taught by Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. having a composition comprising the claimed phospholipids, motivated by the teaching of Ledley that such neutral phospholipids make highly efficient liposomes.

Claims 1-9 lack an inventive step under PCT Article 33(3) as being obvious over Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) in view of Tari et al.

Imperial Cancer Research Technology Limited (WO 93/20200), Brotman, Harns, F. (WO 95/08350) and Tormo et al. are applied as above. None of these references teach liposomes comprising phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a phospholipid selected from a phosphatidylcholine or a phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising an antisense oligonucleotide targeted to Bcl-2 encapsulated in a liposome as taught by Imperial Cancer Research Technology Limited (WO 93/20200) or Brotman, Harns, F. (WO 95/08350) or Tormo et al. and to use the liposomal formulations taught by Tari et al., motivated by the teaching of Tari et al. that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Claims 1-3 and 5-20 lack an inventive step under PCT Article 33(3) as being obvious over Abubakr et al., Pocock et al. and Cotter et al. all in view of Tari et al.

Abubakr et al. teaches (entire document) a SCID mouse model of follicular lymphoma in which WSU-FSCCL cells, which have a t(14:18) translocation, are injected into the mice. Injection of a phosphorothioate antisense oligonucleotide 22 nucleotides long which is targeted to the translation initiation site of Bcl-2 either IP or IV into the mice 3 times a week for 2 weeks starting on day 7 following lymphoma cell injection resulted in a longer survival time and the absence of tumors.

Pocock et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. Constant infusion of an antisense oligonucleotide targeted to Bcl-2 for 14 days starting 8 days after injecting lymphoma cells prevented the development of lymphoma.

Cotter et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. When the cells were pretreated in vitro with an antisense oligonucleotide 20 nucleotides long which is targeted to the translation initiation site of Bcl-2 prior to administration to the mice the development of lymphoma was prevented.

Abubakr et al., Pocock et al, and Cotter et al., taken together, clearly show that treatment of lymphoma cells having a t(14:18) translocation with an antisense oligonucleotide targeted to the translation initiation site of the Bcl-2 gene, either before or after administration to SCID mice, results in the inhibition of proliferation of the lymphoma cells and the prevention of lymphoma development in the mice. None of these references teaches administration of the antisense oligonucleotide as a composition comprising neutral lipids.

Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a neutral phospholipid selected from a phosphatidylcholine or a

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). Tari et al. teaches the benefit of using liposomes consisting of neutral lipids for the delivery of antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). It would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to use an antisense oligonucleotide targeted to Bcl-2 to inhibit the proliferation of cells having a t(14:18) translocation resulting in overexpression of Bcl-2 as taught by Abubakr et al., Pocock et al. and Cotter et al. and to administer the antisense oligonucleotide as a composition comprising a neutral phospholipid as taught by Tari et al., motivated by the teaching of Tari et al. that the neutral lipid composition imparts several benefits on the administration of an antisense oligonucleotide. It further would have been obvious to inhibit the proliferation of a lymphoma cell in a human as effects seen in immunocompromised mouse models of lymphoma and leukemia are recognized in the art to be reasonably predictive of results in humans. In terms of particular volumes, dosages and schedules of administration, one of ordinary skill in the art could practice routine optimization to determine appropriate volumes, dosages and schedules such as those that are claimed when converting treatments developed for mice into equivalent treatments for humans.

Claim 4 lacks an inventive step under PCT Article 33(3) as being obvious over Abubakr et al., Pocock et al. and Cotter et al., all in view of Tari et al. and further in view of Imperial Cancer Research Technology Limited (WO 93/20200).

Abubakr et al., Pocock et al., Cotter et al. and Tari et al. each are applied as above. These references do not teach an antisense oligonucleotide which comprises the sequence of SEQ ID NO:1. Imperial Cancer Research Technology Limited (WO 93/20200) et al. teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). It would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to make and use an antisense oligonucleotide targeted to the translation initiation site of Bcl-2 as taught by Abubakr et al., Pocock et al., Cotter et al. and Tari et al. and to have the oligonucleotide comprise the sequence of SEQ ID NO:1 as taught by Imperial Cancer Research Technology Limited (WO 93/20200) as Abubakr et al., Pocock et al., Cotter et al. and Imperial Cancer Research Technology Limited (WO 93/20200) et al. each teach the targeting of the antisense oligonucleotide to a region comprising the ATG codon of Bcl-2 and all of the references teach an oligonucleotide sequence which comprises at least part of SEQ ID NO:1. Since all of the oligonucleotides overlap and all of them have been shown to be effective they are all equivalent and one of ordinary skill in the art would reasonably expect that any antisense oligonucleotide which comprises SEQ ID NO:1 would work to lower Bcl-2 expression.

NEW CITATIONS

ABUBAKR et al. Effectiveness of BCL-2 antisense oligodeoxynucleotides (AS-ODN) against human follicular small-cleaved cell lymphoma (FSCCL)-SCID mice xenograft model. Blood. December 1994, Vol. 84, No. 10 Suppl. 1, page 374A, Abstract 784, see entire document.

POCOCK et al. In vivo suppression of B-cell lymphoma with BCL-2 antisense oligonucleotides. Blood. December 1993, Vol. 83, No. 10 Suppl. 1, page 200A, Abstract 1481, see entire document.

COTTER et al. Antisense oligonucleotides suppress B-cell lymphoma growth in a SCID-hu mouse model. Oncogene. October 1994, Vol. 9, pages 3049-3055, see entire document.

US 5,417,978 A (TARI et al.) 23 May 1995.

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/127, 31/70, C07H 21/04, C12N 15/00

A1

(11) International Publication Number: WO 98/14172

(43) International Publication Date: 9 April 1998 (09.04.98)

(21) International Application Number: PCT/US97/18348

(22) International Filing Date: 3 October 1997 (03.10.97)

(30) Priority Data:
08/726,211 4 October 1996 (04.10.96) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/726,211 (CIP)
Filed on 4 October 1996 (04.10.96)

(71) Applicant *(for all designated States except US)*: BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TORMO, Mar [ES/ES]; Guillem Sorolla, 36, E-Valencia (ES). TARA, Ana, M. [PT/US]; 7500 Kirby Drive #311, Houston, TX 77030 (US). LOPEZ-BERESTEIN, Gabriel [US/US]; 122 Bellaire Court, Bellaire, TX 77602 (US). MCDONNEL, Timothy, J. [US/US]; 14103 Manderly, Houston, TX 77077 (US).

(74) Agent: CORDER, Timothy, S.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXYNUCLEOTIDES

(57) Abstract

The present invention provides novel compositions and methods for use in the treatment of Bcl-2-associated diseases like cancer, specifically, in the treatment of follicular lymphoma (FL). The compositions contain antisense oligonucleotides that hybridize to Bcl-2 nucleic acids, the gene products of which are known to interact with the tumorigenic protein Bcl-2. Used alone, or in conjunction with other antisense oligonucleotides, these compositions inhibit the proliferation of FL cancer cells.

*(Referred to in PCT Gazette No. 16/1998, Section II)